

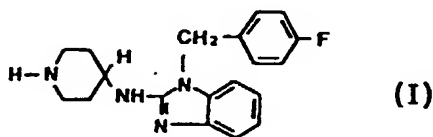
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(54) Title: USE OF NORASTEMIZOLE FOR THE TREATMENT OF ALLERGIC DISORDERS



(57) Abstract

A pharmaceutical composition comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in an anti-histaminic treatment which does not induce any significant cardiac arrhythmia, comprising administering a therapeutically effective amount of the compound of formula (I) to a human patient.

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USE OF NORASTEMIZOLE FOR THE TREATMENT
OF ALLERGIC DISORDERS

5

DESCRIPTION

This invention relates to novel pharmaceutical compositions containing norastemizole. These compositions possess potent antihistaminic activity and are useful in
10 treating allergic rhinitis, asthma and other allergic disorders while avoiding adverse effects associated with the administration of other antihistamines, such as astemizole, including but not limited to cardiac arrhythmias, drowsiness, nausea, fatigue, weakness and headache. Also, these
15 compositions, in combination with non-steroidal anti-inflammatory agents or other non-narcotic analgesics, are useful for the treatment of cough, cold, cold-like, and/or flu symptoms and the discomfort, headache, pain, fever, and general malaise associated therewith. The aforementioned combinations may
20 optionally include one or more other active components including a decongestant, cough suppressant/antitussive, or expectorant.

Additionally, these novel pharmaceutical compositions containing norastemizole are useful in treating motion sickness, vertigo, diabetic retinopathy, small vessel
25 complications due to diabetes and such other conditions as may be related to the activity of these derivatives as antagonists of the H-1 histamine receptor while avoiding the adverse effects associated with the administration of other antihistamines, such as astemizole.

30 Also disclosed are methods for treating the above-described conditions in a human while avoiding the adverse effects that are associated with the administration of other antihistamines, such as astemizole, by administering the aforementioned pharmaceutical compositions containing
35 norastemizole to said human.

The active compound of these compositions and methods is a metabolic derivative of astemizole. Chemically, this derivative is norastemizole. This compound is described in

Kamei et al., Arzneimittel-Forschung/Drug Research, 41: 932-36 (1991).

Astemizole is an antagonist of the H-1 histamine receptor protein. Histamine receptor proteins occur in two well-identified forms in tissues as H-1 and H-2 receptors. The H-1 receptors are those that mediate the response antagonized by conventional antihistamines. H-1 receptors are present, for example, in the ileum, the skin, and the bronchial smooth muscle of man and other mammals. Astemizole antagonizes the effect of histamine in the guinea pig isolated ileum, suppresses histamine-induced whealing in the skin of guinea pigs, and protects against histamine induced bronchoconstriction in the guinea pig.

Through H-2 receptor-mediated responses, histamine stimulates gastric acid secretion in mammals and the chronotropic effect in isolated mammalian atria. Astemizole has no effect on histamine-induced gastric acid secretion, nor does it alter the chronotropic effect of histamine on atria. Thus, astemizole has no apparent effect on the H-2 histamine receptor.

Astemizole is well absorbed but is extensively metabolized. See Uchiyama et al., Pharmacometrics, 40: 77-93 (1990). Three main metabolites have been identified, and all of the metabolites are reported to have antihistaminic activity. See Kamei et al., Arzneimittel-Forschung/Drug Research, 41: 932-36 (1991).

On the basis of its antihistaminic activity, researchers evaluated the pharmacological effects of astemizole in man. Clinical trials of efficacy indicated that astemizole is an effective H-1 antagonist. See Howarth, Clin. Exp. Allergy, 20 (Suppl. 2): 31-41 (1990).

Weintraub et al., Hosp. Formul., 22: 918-27 (1987) describes clinical efficacy of astemizole in the treatment of both seasonal and perennial allergies. It has also been suggested that astemizole would be useful for the treatment of asthma.

Astemizole may also be useful for the treatment of motion sickness and vertigo. Some antihistamines have been found to be effective for the prophylaxis and treatment of motion sickness. See Wood, Drugs, 17: 471-479 (1979). Some

antihistamines have also proven useful for treating vestibular disturbances, such as Meniere's disease, and in other types of vertigo. See Cohen et al., Archives of Neurology, 27: 129-135 (1972).

5 In addition, astemizole may be useful in the treatment of diabetic retinopathy and other small vessel disorders associated with diabetes mellitus. In tests on rats with streptozocin-induced diabetes, treatment by antihistamines prevented the activation of retinal histamine receptors which
10 have been implicated in the development of diabetic retinopathy. The use of antihistamines to treat retinopathy and small vessel disorders associated with diabetes mellitus is disclosed in U.S. Patent No. 5,019,591.

Many antihistamines cause somewhat similar adverse
15 effects. These adverse effects include but are not limited to sedation, gastrointestinal distress, dry mouth, and constipation or diarrhea. Astemizole has been found to cause relatively less sedation as compared with other antihistamines. See Weintraub et al., Hosp. Formul., 22: 918-27 (1987).

20 However, the administration of astemizole to a human has been found to cause other adverse effects. These adverse effects include but are not limited to cardiac arrhythmias, including ventricular tachyarrhythmias, torsades de pointes, and ventricular fibrillation. Recently, clinical practitioners have
25 noted an increase in the occurrence of these cardiac arrhythmias upon co-administration of astemizole with other drugs such as ketoconazole and erythromycin or upon overdose of astemizole. See Knowles, Canadian Journal Hosp. Pharm., 45: 33,37 (1992); Craft, British Medical Journal, 292: 660 (1986); Simons et al.,
30 Lancet, 2: 624 (1988); and Unknown, Side Effects of Drugs Annual, 12: 142 and 14: 135. An additional unwanted side effect of astemizole is appetite stimulation and weight gain in patients taking the drug for various indications. See Krstenansky et al., Drug Intell. Clin. Pharm., 21: 947-53
35 (1987).

Thus, it would be particularly desirable to find a compound with the advantages of astemizole which would not have the aforementioned disadvantages.

It has now been discovered that norastemizole (a metabolic derivative of astemizole) is an effective antihistamine. It has also been discovered that pharmaceutical compositions containing norastemizole are useful in treating 5 allergic disorders and such other conditions as may be related to the composition's activity as an antihistamine, including but not limited to allergic rhinitis, solar urticaria, and symptomatic dermographism.

Furthermore, it has now also been discovered that 10 norastemizole is useful in treating asthma. Also, norastemizole is useful for the treatment of motion sickness and vertigo and in treating such disorders as retinopathy and small vessel disorders associated with diabetes mellitus.

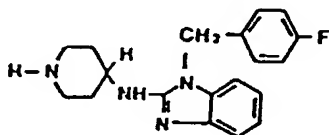
The present invention also includes methods for 15 treating the above-described conditions in a human, while avoiding the adverse effects that are associated with astemizole, including but not limited to cardiac arrhythmias, sedation, gastrointestinal distress, dry mouth, and constipation or diarrhea, by administering norastemizole to said human.

20 It has also been discovered that norastemizole, in combination with non-steroidal anti-inflammatory agents or other non-narcotic analgesics, is useful for the treatment of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, headache, fever, and general malaise associated therewith. The 25 use of pharmaceutical compositions of the invention, containing (1) norastemizole and (2) non-narcotic analgesics or non-steroidal anti-inflammatory agents such as aspirin, acetaminophen or ibuprofen, may optionally include one or more other active components including a decongestant (such as 30 pseudoephedrine), a cough suppressant/antitussive (such as dextromethorphan) or an expectorant (such as guaifenesin).

The present invention encompasses a method of treating a human afflicted by or susceptible to an allergic disorder while avoiding the concomitant liability of adverse 35 effects associated with the administration of astemizole, which comprises administering to said human afflicted by or susceptible to an allergic disorder an amount of norastemizole, or a pharmaceutically acceptable salt thereof, said amount being sufficient to treat said allergic disorder, but

insufficient to cause the adverse effects associated with astemizole.

Accordingly and in a first aspect, the present invention provides a pharmaceutical composition comprising 5 norastemizole, the structure of which is depicted by formula I:



10

or a pharmaceutically acceptable salt thereof, for use in an anti-histaminic treatment which does not induce any significant cardiac arrhythmia, comprising administering a therapeutically 15 effective amount of the compound of formula I to a human patient.

Prior to the present invention, those skilled in the art would have expected compounds of formula I to have induced a form of cardiac arrhythmia known as torsades de pointes (as 20 reported by Brian P. Monahan et. al., in JAMA, 5th Dec 1990, Vol. 264, No. 21, pp. 2788-90, and Sandra Knowles in The Canadian Journal of Hospital Pharmacy, Vol. 45, No. 1, 1 Feb 1992, p.33), since this potentially lethal arrhythmia was considered to be a "class effect" among non-sedating 25 antihistamines, in the sense that the arrhythmogenicity was considered to be coupled to the anti-histaminic potency of such compounds. Accordingly, the fact that the compositions, in accordance with the present invention, do not induce any such cardiac arrhythmias is a new, highly useful and surprising 30 technical effect, which enables the inventive compositions to be administered to individuals susceptible to cardiac arrhythmia, and in potentially larger doses than those non-sedating anti-histamines, such as astemizole, in common use at the present time.

35 The anti-histaminic treatment can be a method of treating a human afflicted by or susceptible to: an allergic disorder; motion sickness; vertigo; retinopathy, or another small vessel disease associated with diabetes mellitus; cough, cold, cold-like or flu symptoms; or the discomfort, pain, fever

or general malaise associated therewith. In embodiments, the invention can relate to any one, any combination, or all of the aforementioned methods of treatment.

Preferably, the invention relates to the treatment
5 of an allergic disorder which is manifested by asthma or allergic rhinitis.

In preferred embodiments, the treatments of the invention comprise the administration of the compound of formula I, in an amount of 1-200mg/day and, preferably, in an amount of
10 5-50mg/day.

In preferred embodiments, the inventive composition further comprises a pharmaceutically acceptable carrier or excipient.

Particularly when the anti-histaminic treatment is
15 that of cough, cold, cold-like, or flu symptoms or the discomfort, pain, fever or general malaise associated therewith, in a human, the composition can further comprise a therapeutically effective amount of a non-steroidal anti-inflammatory agent or non-narcotic analgesic, such as
20 acetylsalicylic acid, acetaminophen, ibuprofen, ketoprofen, or naproxen, or a pharmaceutically acceptable salt thereof. Alternatively, or additionally, a composition in accordance with the present invention can further comprise a therapeutically effective amount of a decongestant, such as pseudoephedrine, or
25 a pharmaceutically acceptable salt thereof.

In a preferred embodiment, the inventive composition comprises from 5mg to 50mg of the compound of formula I and from 25mg to 600mg of an anti-inflammatory agent or an analgesic. When the inventive composition comprises a therapeutically
30 effective amount of a decongestant, it, preferably, comprises from 5mg to 50mg of the compound of formula I and from 5mg to 150mg of the decongestant.

In a second aspect, the invention relates to a method of providing an anti-histaminic treatment which does not
35 induce any significant cardiac arrhythmia, to a human patient, comprising administering a therapeutically effective amount of a pharmaceutical composition in accordance with the first aspect of the invention, preferably, in one of its preferred embodiments, to said human patient. Preferably, the inventive

method is a method of treating a human afflicted by or susceptible to: an allergic disorder; motion sickness; vertigo; retinopathy, or another small vessel disease associated with diabetes mellitus; cough, cold, cold-like or flu symptoms; or the discomfort, pain, fever or general malaise associated therewith. Preferably, the method is a method for treating a human afflicted by or susceptible to an allergic disorder and, more preferably, the allergic disorder is asthma or allergic rhinitis.

10 In a third aspect, the invention relates to a use of a composition, in accordance with the first aspect of the invention, or any of its preferred embodiments, for the manufacture of a medicament for use in an anti-histaminic treatment which does not induce any significant cardiac
15 arrhythmia, comprising administering a therapeutically effective amount of the compound to a human patient. Preferably, said use is for the manufacture of a medicament for use in a method of treating a human afflicted by or susceptible to: an allergic disorder; motion sickness; vertigo; retinopathy, or another
20 small vessel disease associated with diabetes mellitus; cough, cold, cold-like or flu symptoms; or the discomfort, pain, fever or general malaise associated therewith. More preferably, said method is a method of treating a human afflicted by or susceptible to an allergic disorder which, preferably, is
25 manifested by asthma or allergic rhinitis.

Astemizole has antihistaminic activity and provides therapy and a reduction of symptoms for a variety of conditions and disorders related to allergic disorders, diabetes mellitus and other conditions; however, this drug, while offering the
30 expectation of efficacy, causes adverse effects. Utilizing norastemizole results in diminished adverse effects, and accordingly, an improved therapeutic index. It is, therefore, more desirable to use norastemizole than to use astemizole itself. Indeed, norastemizole may be administered in greater
35 doses than would be appropriate for astemizole.

The term "adverse effects" includes, but is not limited to, cardiac arrhythmias, cardiac conduction disturbances, appetite stimulation, weight gain, sedation, gastrointestinal distress, dry mouth, constipation, and

diarrhea. The term "cardiac arrhythmias" includes, but is not limited to, ventricular tachyarrhythmias, torsades de pointes, and ventricular fibrillation.

The phrase "therapeutically effective amount" means
5 that amount of a compound of the invention which provides a therapeutic benefit in an antihistaminic treatment, including the treatment or management of allergic disorders, asthma, retinopathy or other small vessel disorders associated with diabetes mellitus, motion sickness, vertigo, or cough, cold,
10 cold-like, and/or flu symptoms and the discomfort, pain, fever, and general malaise associated therewith. Examples of allergic disorders include, but are not limited to, allergic rhinitis, solar urticaria, and symptomatic dermographism. The symptoms associated with these allergic disorders and the cough, cold,
15 cold-like, and/or flu symptoms include, but are not limited to, sneezing, rhinorrhea, lacrimation, and dermal irritation. The term "asthma" is defined as a disorder characterized by increased responsiveness of the trachea and bronchi to various stimuli which results in symptoms which include wheezing, cough,
20 and dyspnea. The term "vertigo" as used herein means the dizziness associated with, but not limited to, motion, height, and changes in body position. The term "diabetic retinopathy" or "retinopathy associated with diabetes mellitus" is that disorder caused by increased permeability of the capillaries in
25 the eye which leads to hemorrhages and edema in the eye and can lead to blindness. The term "small vessel disorders associated with diabetes mellitus" includes, but is not limited to, diabetic retinopathy and peripheral vascular disease.

The magnitude of a prophylactic or therapeutic dose
30 of norastemizole in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily
35 dose range, for the conditions described herein, is from about 1 mg to about 200 mg administered in single or divided doses orally, topically, transdermally, or locally by aerosol. For example, a preferred oral daily dose range should be from about 5 mg to about 50 mg. It is further recommended that children,

patients aged over 65 years, and those with impaired renal or hepatic function initially receive low doses, and that they then be titrated based on individual response(s) or blood level(s).

It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

The various terms "an amount sufficient to alleviate said allergic disorder but insufficient to cause said adverse effects," "an amount sufficient to alleviate said asthma but insufficient to cause said adverse effects," "an amount sufficient to alleviate said motion sickness but insufficient to cause said adverse effects," and "an amount sufficient to alleviate said retinopathy or other small vessel diseases associated with diabetes mellitus but insufficient to cause said adverse effects" are encompassed by the above-described dosage amounts and dose frequency schedule. In addition, the terms "a pharmaceutical composition for use in the treatment of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, fever and general malaise associated therewith, in a human, said composition comprising (i) a therapeutically effective amount of norastemizole, with (ii) a therapeutically effective amount of at least one non-steroidal anti-inflammatory agent or non-narcotic analgesic" and "a pharmaceutical composition for use in the treatment of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, fever and general malaise associated therewith, in a human, said composition comprising (i) a therapeutically effective amount of norastemizole, with (ii) a therapeutically effective amount of a decongestant" are also encompassed by the above-described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage of norastemizole. For example, oral, rectal, parenteral, transdermal, subcutaneous, intramuscular, and like forms of administration may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, and the like.

The pharmaceutical compositions of the present invention comprise norastemizole as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other
5 therapeutic ingredients.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases, including inorganic or organic acids or bases. Examples of such inorganic acids are hydrochloric, hydrobromic,
10 hydroiodic, sulfuric, and phosphoric. Appropriate organic acids may be selected, for example, from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic,
15 salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic, stearic, sulfanilic, algenic, and galacturonic. Examples of such inorganic bases include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc.
20 Appropriate organic bases may be selected, for example, from N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), lysine and procaine.

The compositions of the present invention include
25 compositions such as suspensions, solutions and elixirs; aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like, in the case of oral solid preparations (such as powders, capsules, and tablets), with the
30 oral solid preparations being preferred over the oral liquid preparations. The most preferred oral solid preparations are tablets.

Because of their ease of administration, tablets and capsules represent advantageous oral dosage unit forms, in which
35 case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of the present invention may also be

administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719.

Pharmaceutical compositions of the present invention
5 suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, or aerosol sprays, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion,
10 or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are
15 prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

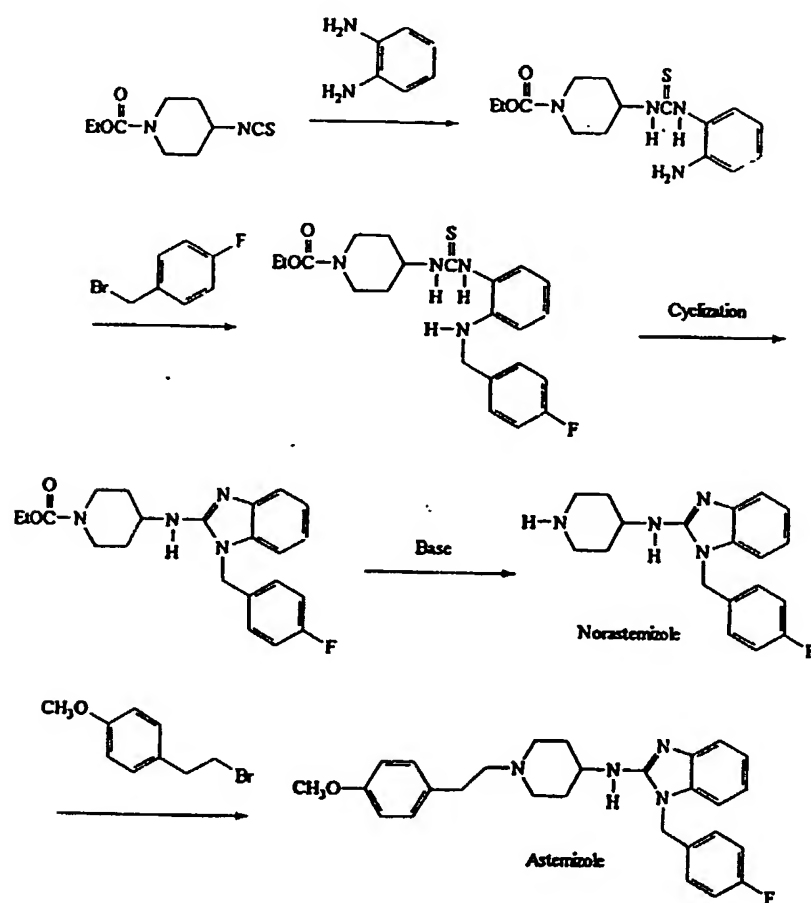
For example, a tablet may be prepared by
20 compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent.
25 Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 5 mg to about 150 mg of the active ingredient, and each cachet or capsule contains from about 5 mg to about 150 mg of the active
30 ingredient, i.e., norastemizole. Most preferably, the tablet, cachet or capsule contains either one of three dosages, 5 mg, 10 mg or 20 mg of the active ingredient.

The invention is further defined by reference to the following examples describing in detail the preparation of the
35 compounds and the compositions of the present invention, as well as their utility. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced which are within the scope of this invention.

EXAMPLESExample 1Preparation of Astemizole and Norastemizole

- 5 Astemizole can be synthesized by methods disclosed in U.S. Patent No. 4,219,559. Norastemizole is prepared similarly, by reaction steps conventional in the art, as depicted below:

10



Reaction of the isothiocyanate shown with phenylenediamine gives the corresponding thiourea. N-Alkylation with *p*-fluorobenzylbromide gives the secondary amine which, upon cyclization, yields the substituted benzimidazole shown.

- 5 Treatment of the benzimidazole with base hydrolyzes the urethane moiety to give norastemizole. N-Alkylation of norastemizole with *p*-methoxyphenethyl bromide yields astemizole.

Example 2

10

Activities of astemizole and norastemizole at the histamine H₁-receptor were assessed using the [³H]pyrilamine binding assay as described in Chang et al., J. Neurochem. 32: 1653-1663 (1979). Briefly, membranes from bovine cerebellum
15 were incubated with [³H]pyrilamine and varying concentrations of test compound. The reactions were carried out in 50 mM sodium phosphate buffer (pH 7.5) at 25° C for 30 minutes. The reaction was terminated by rapid vacuum filtration onto glass fiber
20 filters. Radioactivity trapped on the filters was determined and compared to control values to ascertain the interaction of the test compound with the H₁-receptor.

The metabolite (norastemizole) is approximately 100 times more potent than the parent compound (astemizole).

25

Example 3

A laboratory investigation was performed to study the comparative propensities of astemizole and norastemizole to induce a form of cardiac arrhythmia, namely torsades de pointes,
30 which results from prolongation of the cardiac action potential duration ("APD"). Such lethal arrhythmias are the most serious side effect known for astemizole.

Cats weighing 2-3 kg were anesthetized and heparinized. The heart was quickly removed through a mid-
35 sternal thoracotomy and cannulated for retrograde perfusion in a "Langendorff apparatus." Temperature was kept at 37°C and pacing electrodes were placed in the right ventricular apex and stimulated at 400 msec cycle length. The AV node was destroyed by cautery to produce complete heart block and allow

observations at slow cycle lengths. Electrodes were placed in the bath and positioned for recording of an ECG that allowed accurate measurement of the QT interval. Monophasic action potential ("MAP") catheters were placed on the left ventricular surface for recording of the duration of the cardiac action potential. All data were stored on a video recorder for later analysis.

After 20 minutes of stabilization, the QT interval and MAP duration were observed until three separate recordings (2-3 minutes apart) indicated the presence of stable measurements (<5% changes). After pre-drug recordings of QT and MAP had been obtained, the perfusion solution was changed to include astemizole or norastemizole. QT and MAP recordings were obtained continuously for at least 40 minutes at each drug concentration to obtain stable readings.

Initially, the hearts were perfused with concentrations of astemizole at 1 to 10 μM , but since astemizole proved to be more potent than anticipated in prolonging APD and QT, additional experiments were run at a lower concentration (0.5 μM).

Every five minutes throughout the study, the QT interval and MAP duration were measured for three cardiac cycles. Beats were selected that provided artifact-free tracings, and the QT and MAP at 90% repolarization (MAP_{90}) were recorded for each beat. The mean of the three measurements for each 5-minute period were calculated. The effects of increasing concentration on QT and MAP_{90} were analyzed and tabulated.

The results are summarized in the following table, from which it is apparent that astemizole potently prolongs the QT interval (and APD duration). At concentrations of 0.5 to 1.0 μM , astemizole prolonged the action potential duration by 20 to 25%. Norastemizole caused similar electrophysiological effects, but only at concentrations of 10 μM . Thus, astemizole was 10 to 20 times more potent than norastemizole in prolonging the cardiac action potential.

Prolongation by astemizole and norastemizole
of QT interval and APD₉₀ duration

5	ASTEMIZOLE (Mean \pm Standard Deviation)		
	CONC. (μ M)	QT %; (N)	APD ₉₀ %; (N)
10	0.5	20; (1)	25; (1)
	1.0	24 \pm 5; (3)	23 \pm 5; (3)
	5.0	43 \pm 19; (3)	40 \pm 12; (4)
15	10.0	47; (1)	45; (1)

20	NORASTEMIZOLE (Mean \pm Standard Deviation)		
	CONC. (μ M)	QT %; (N)	APD ₉₀ %; (N)
25	0.5	4; (1)	2; (1)
	1.0	6 \pm 2; (4)	6 \pm 3; (4)
	5.0	17 \pm 6; (5)	13 \pm 6; (5)
30	10.0	28 \pm 10; (5)	19 \pm 12; (5)

35

Because norastemizole was up to 100 times more potent than
astemizole as an antihistaminic, while norastemizole was 10 or
40 20 times less potent in causing the serious arrhythmogenic side
effect known to be associated with the drug, it is concluded
that norastemizole has a therapeutic index on the order of up to
1000 to 2000 times higher than the therapeutic index of the
parent compound.

45

Example 4Oral Formulation - Capsules:

5 Formula	Quantity per capsule in mg.		
	A	B	C
Active ingredient			
10 Astemizole metabolite	5.0	10.0	20.0
Starch 1500	94.0	89.0	79.0
15 Magnesium Stearate BP	1.0	1.0	1.0
Compression Weight	100.0	100.0	100.0

20 The active ingredient is sieved and blended with the excipients. The mixture is filled into suitably sized two-piece hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and if necessary, changing the capsule size to suit.

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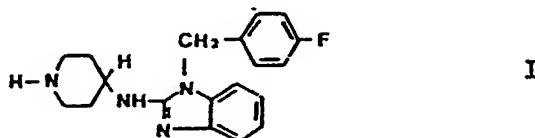
Example 5Oral Formulation - Tablets:

30 Formula	Quantity per Tablet in mg.		
	A	B	C
Active ingredient,			
35 Astemizole metabolite	5.0	10.0	20.0
Lactose BP	148.5	143.5	133.5
Starch BP	30.0	30.0	30.0
40 Pregelatinized Maize Starch BP	15.0	15.0	15.0
Magnesium stearate	1.5	1.5	1.5
45 Compression Weight	200.0	200.0	200.0

The active ingredient is sieved through a suitable sieve and blended with the lactose until a uniform blend is formed. Suitable volumes of water are added and the powders are granulated. After drying, the granules are then screened and 5 blended with the magnesium stearate. The resulting granules are then compressed into tablets of desired shape. Tablets of other strengths may be prepared by altering the ratio of active ingredient to the excipient(s) or the compression weight.

CLAIMS:

1. A pharmaceutical composition comprising the compound
5 of formula I:



- 10 or a pharmaceutically acceptable salt thereof, for use in an
anti-histaminic treatment which does not induce any significant
cardiac arrhythmia, comprising administering a therapeutically
effective amount of the compound of formula I to a human
patient.

15

2. A pharmaceutical composition, as claimed in claim 1,
wherein the anti-histaminic treatment is a method of treating a
human afflicted by or susceptible to: an allergic disorder;
motion sickness; vertigo; retinopathy or other small vessel
20 diseases associated with diabetes mellitus; cough, cold, cold-
like or flu symptoms; or the discomfort, pain, fever or general
malaise associated therewith.

3. A pharmaceutical composition, as claimed in claim 2,
25 wherein the allergic disorder is manifested by asthma or
allergic rhinitis.

4. A pharmaceutical composition, as claimed in any of
the preceding claims, wherein the anti-histaminic treatment
30 comprises the administration of a compound of formula I in an
amount of 1-200mg/day and, preferably, in an amount of 5-
50mg/day.

5. A pharmaceutical composition, as claimed in any of
35 the preceding claims, further comprising a pharmaceutically
acceptable carrier or excipient.

6. A pharmaceutical composition, as claimed in any of
the preceding claims, further comprising a therapeutically

effective amount of a non-steroidal anti-inflammatory agent or a non-narcotic analgesic.

7. A pharmaceutical composition, as claimed in claim 6,
5 comprising from 5mg to 50mg of the compound of formula I and
from 25mg to 600mg of the anti-inflammatory agent or analgesic.

8. A pharmaceutical composition, as claimed in any of
the preceding claims, further comprising a therapeutically
10 effective amount of a decongestant.

9. A pharmaceutical composition, as claimed in claim 8,
comprising from 5mg to 50mg of the compound of formula I and
from 5mg to 150mg of a decongestant.

15

10. A method of providing an anti-histaminic treatment
which does not induce any significant cardiac arrhythmia, to a
human patient, comprising administering a therapeutically
effective amount of a pharmaceutical composition, as claimed in
20 any of claims 1-9, to said human patient.

11. A method as claimed in claim 10, wherein the
treatment is a method of treating a human afflicted by or
susceptible to: an allergic disorder; motion sickness; vertigo;
25 retinopathy or other small vessel diseases associated with
diabetes mellitus; cough, cold, cold-like or flu symptoms; or
the discomfort, pain, fever or general malaise associated
therewith.

30 12. A method, as claimed in claim 11, wherein the
allergic disorder is manifested by asthma or allergic rhinitis.

13. Use of a composition, as claimed in any of claims 1-
9, for the manufacture of a medicament for use in an anti-
35 histaminic treatment which does not induce any significant
cardiac arrhythmia, comprising administering a therapeutically
effective amount of the compound of formula I to a human
patient.

14. A use, as claimed in claim 13, wherein the treatment is a method of treating a human afflicted by or susceptible to: an allergic disorder; motion sickness; vertigo; retinopathy or other small vessel diseases associated with diabetes mellitus;
5 cough, cold, cold-like or flu symptoms; or the discomfort, pain, fever or general malaise associated therewith.

15. A use, as claimed in claim 14, wherein the allergic disorder is manifested by asthma or allergic rhinitis.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 93/08349

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
1 X	ARZNEIMITTEL FORSCHUNG vol. 41, no. II, September 1991 pages 932 - 936 KAMEI, C. ET AL 'ANTIALLERGIC EFFECTS OF MAJOR METABOLITES OF ASTEMIZOLE IN RATS AND GUINEA PIGS' cited in the application see the whole document	1-5, 10-15
2 X	EP,A,0 232 937 (JANSSEN PHARMACEUTICA N.V.) 19 August 1987 see the whole document especially page 14-15, table III, compounds 112 & 137; page 22-23, example 5	1-5, 10-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "A" document member of the same patent family

Date of the actual completion of the international search

26 November 1993

Date of mailing of the international search report

08.12.93

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Mair, J

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/08349

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 10-12 are directed towards a method of treatment of the human/animal body, the search has been carried out and based upon the alleged effects of the compositions.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 93/08349

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0232937	19-08-87	AU-B- 583706	04-05-89
		AU-A- 6821887	06-08-87
		DE-A- 3781173	24-09-92
		JP-A- 62215575	22-09-87
		US-A- 4835161	30-05-89
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